REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The specification has been amended to include sequence identifiers. The claims have been revised to define the invention with additional clarity.

The Examiner indicates that the oath/declaration is defective. Respectfully, basis for the Examiner's assertion is not seen. The declaration used here is that viewed by the Office as acceptable in the now issued parent case (USP 6,307,126).

On page 3 of the Action (item 4), the Examiner objects to the claims. The objections are moot in view of the above-noted claim revisions.

Claims 49-69 stand rejected as allegedly representing obviousness-type double patenting over claims of USP 6,307,126. In order to advance prosecution, submitted herewith is a Terminal Disclaimer that moots the rejection.

Claims 50 and 52-69 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is in order for the reasons that follow.

As regards the term "antagonised", it simply takes its normal meaning as understood in the chemical and biological

fields. An antagonist of an activity, e.g., enzymatic activity of a protein or, here, inhibition of growth of a plant, opposes that activity. It does not necessarily "reverse" or "overcome" that activity: the magnitude of the antagonism may be dose-dependent. Basis for the Examiner's concern is not seen and clarification is requested.

In claim 52, "is" has been replaced with --as--, in accordance with the Examiner's suggestion.

Claims 52-54 have been revised to refer to hybridization to the complement of the nucleic acid, as the Examiner suggests, and to include hybridization conditions from Peng et al., *Plant Cell* 5, 351-360 (1993), which is reference 5 in the application and is of record.

The objection to claims 59 and 69 appears to be inconsistent with the granted claims in the parent case. Thus, no amendment is believed necessary and none has been made.

In claim 62, the words "or derivative" have been deleted.

The Examiner's objection to claim 69 is again apparently inconsistent with the parent granted claim 20. Thus no revision is believed necessary.

Reconsideration is requested.

Claims 49 and 52-69 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Claims 49-69 also stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejections is believed to be in order in view of the above claim revisions (specifically, that relating to the hybridization language of claims 52-54) and further in view of the comments that follow.

The Examiner refers to the 17 amino acid sequence for which functional significance is described and demonstrated in the application, and states: "While 17 amino acids have been deleted, the gai mutant still shares greater than 90% amino acid identity with SEQ ID NO:2. It is then apparent that nucleotide sequences encoding polypeptides that have at least 90% amino acid identity with SEQ ID NO:2 do not all possess the functional activity of SEQ ID NO:2. The structure of the claimed nucleic acids are then not correlated with the function of SEQ ID NO:2."

The claims have been amended to require the presence of the 17 amino acid sequence that Applicants demonstrated is required for function. (The counterpart mutants in which the 17 amino acid sequence is deleted are claimed separately in the co-pending application 09/911,514, filed

as a divisional from the common parent application in the light of the Examiner's restriction requirement.)

The levels of sequence identity or hybridization requirements as set out in the claims define only a narrow genus of sequences that have a close relationship with the precise sequence SEQ ID NO:2 set forth in the application. The experiments described demonstrate that the presence or absence of the defined 17 amino acid sequence is functionally significant: sequences containing the 17 amino acid sequence inhibit plant growth in a manner that is antagonized by gibberellin, and are able to complement a *GAI* null mutant phenotype in a plant, while mutants that lack the 17 amino acid sequence confer a dwarfed phenotype on plants compared with wild-type, and this effect is gibberellin-insensitive.

The claims define a narrow genus by sequence, structure and function. That Applicants were in possession of this genus when the application was filed is reflected by the disclosure in the specification. Various alleles and mutants and described and discussed. Homologous sequences have been found in various species, including *Zea Mays* (maize), *O. Sativa* (rice), and *Brassica napus* (rape). The disclosure is fully enabling of the reasonable claim

scope given the sequence, structure and function elements in the claims.

The situation here is distinct from that in Fiers. Here, much more is provided than a mere statement that certain sequences are part of the invention. The Examiner's assertions to the contrary, an adequate description is provided of the narrow genus defined by the claims and that genus is supported by species in the disclosure.

Given the nature of Applicants' invention and the disclosure provided, to require limitation of the claims would be to unduly restrict Applicants in the scope of protection to which they are rightly entitled.

In addition to the above, the Examiner's attention is directed to the fact that a search of the claims database reveals that numerous patents have issued (based on disclosures comparable to that provided here - or less) that recite 90% (or less) sequence identify.

Reconsideration is requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

HARBERD et al -- Serial No.: 09/911,513

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE, P.C.

By Mary J. Wilson
Mary J. Wilson
Reg. No. 32,955

MJW:tat

1100 North Glebe Road
8th Floor
Arlington, Virginia 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 7, line 10:

A preferred nucleotide sequence for a *GAI* gene is one which encodes amino acid sequence shown in Figure 4 (SEQ ID NO:2), especially a coding sequence shown in Figure 3 (SEQ ID NO:1). A preferred *gai* mutant lacks part or all of the 17 amino acid sequence underlined in Figure 4.

The paragraph beginning at page 10, line 10:

Since the GAI amino acid sequence of Arabidopsis shown in Figure 4 (SEQ ID NO:2) includes 5 consecutive histidines close to its N-terminus, substantial purification of GAI or gai may be achieved using Ni-NTA resin available from QIAGEN Inc. (USA) and DIAGEN GmbH (Germany). See Janknecht et al[31] and EP-A-0253303 and EP-A-0282042. Ni-NTA resin has high affinity for proteins wiht consecutive histidines close to the N- or C-terminus of the protein and so may be used to purifiy GAI or gai proteins from plants, plant

parts or extracts or from recombinant organisms such as yeast or bacteria, e.g. *E. coli*, expressing the protein.

The paragraph beginning at page 11, line 18:

Antibodies raised to a GAI, or gai, polypeptide can be used in the identification and/or isolation of homologous polypeptides, and then the encoding genes. Thus, the present invention provides a method of identifying or isolating a polypeptide with GAI function or ability to confer a *gai* mutant phenotype, comprising screening candidate polypeptides with a polypeptide comprising the antigen-binding domain of an antibody (for example whole antibody or a fragment thereof) which is able to bind an *Arabidopsis* GAI or gai polypeptide, or preferably has binding specificity for such a polypeptide, such as having the amino acid sequence shown in Figure 4 (SEQ ID NO:2).

The paragraph beginning at page 12, line 19:

A further aspect of the present invention provides a method of identifying and cloning GAI homologues from plant species other than *Arabidopsis thaliana* which method employs a nucleotide sequence derived from that shown in

Figure 3 (SEQ ID NO:1). Sequences derived from these may themselves be used in identifying and in cloning other sequences. The nucleotide sequence information provided herein, or any part thereof, may be used in a data-base search to find homologous sequences, expression products of which can be tested for *GAI* function. Alternatively, nucleic acid libraries may be screened using techniques well known to those skilled in the art and homologous sequences thereby identified then tested.

The paragraphs beginning at page 13, line 14:

In a preferred embodiment of this aspect of the present invention, the nucleic acid used for probing of candidate nucleic acid encodes an amino acid sequence shown in Figure 4 (SEQ ID NO:2), a sequence complementary to a coding sequence, or a fragment of any of these, most preferably comprising a nucleotide sequence shown in Figure 3 (SEQ ID NO:1).

Alternatively, as discussed, a probe may be designed using amino acid sequence information obtained by sequencing a polypeptide identified as being able to be bound by an antigen-binding domain of an antibody which is

able to bind a GAI or gai polypeptide such as one with the amino acid sequence shown in Figure 4 (SEQ ID NO:2).

The paragraph beginning at page 14, line 21:

The present invention also extends to nucleic acid encoding a *GAI* homologue obtained using a nucleotide sequence derived from that shown in Figure 3 (SEQ ID NO:1).

The paragraph beginning at page 15, line 1:

Homology may be at the nucleotide sequence and/or amino acid sequence level. Preferably, the nucleic acid and/or amino acid sequence shares homology with the sequence encoded by the nucleotide sequence of Figure 3 (SEQ ID NO:1), preferably at least about 50%, or 60%, or 70%, or 80% homology, most preferably at least 90% or 95% homology. Nuleic acid encoding such a polypeptide may preferably share with the *Arabidopsis thaliana GAI* gene the ability to confer a particular phenotype on expression in a plant, preferably a phenotype which is GA responsive (i.e. there is a change in a characteristic of the plant on treatment with GA), such as the ability to inhibit plant growth where the inhibition is antagonised by GA. As noted,

GAI expression in a plant may affect one or more other characteristics of the plant. A preferred characteristic that may be shared with the *Arabidopsis thaliana GAI* gene is the ability to complement a *GAI* null mutant phenotype in a plant such as *Arabidopsis thaliana*, such phenotype being resistance to the dwarfing effect of paclobutrazol.

The paragraphs beginning at page 16, line 3:

As is well-understood, homology at the amino acid level is generally in terms of amino acid similarity or identity. Similarity allows for "conservative variation", i.e. substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as arginine for lysine, glutamic for aspartic acid, or glutamine for asparagine. Similarity may be as defined and determined by the TBLASTN program, of Altschul et al. (1990) *J. Mol. Biol.* 215: 403-10, which is in standard use in the art. Homology may be over the full-length of the *GAI* sequence of Figure 4 (SEQ ID NO:2), or may more preferably be over a contiguous sequence of 17 amino acids, compared with the 17 amino acids underlined in Figure 4, or a longer sequence, e.g. about 20, 25, 30, 40, 50 or more amino

acids, compared with the amino acid sequence of Figure 4 (SEQ ID NO:2) and preferably including the underlined 17 amino acids.

At the nucleic acid level, homology may be over the full-length or more preferably by comparison with the 51 nucleotide coding sequence within the sequence of Figure 3 (SEQ ID NO:1) and encoding the 17 amino acid sequence underlined in Figure 4, or a longer sequence, e.g. about, 60, 70, 80, 90, 100, 120, 150 or more nucleotides and preferably includeing the 51 nucleotide of Figure 3 (SEQ ID NO:1) which encodes the underlined 17 amino acid sequence of Figure 4.

The paragraph beginning at page 17, line 16:

A further aspect of the present invention provides a nucleic acid isolate having a nucleotide sequence encoding a polypeptide which includes an amino acid sequence which is a mutant, allele, derivative or variant sequence of the GAI amino acid sequence of the species *Arabidopsis thaliana* shown in Figure 4 (SEQ ID NO:2), or is a homologue of another species or a mutant, allele, derivative or variant thereof, wherein said mutant, allele, derivative, variant

or homologue differs from the amino acid sequence shown in Figure 4 (SEQ ID NO:2) by way of insertion, deletion, addition and/or substitution of one or more amino acids, as obtainable by producing transgenic plants by transforming plants which have a *GAI* null mutant phenotype, which phenotype is resistance to the dwarfing effect of paclobutrazol, with test nucleic acid, causing or allowing expression from test nucleic acid within the transgenic plants, screening the transgenic plants for those exhibiting complementation of the *GAI* null mutant phenotype to identify test nucleic acid able to complement the GAI null mutant, deleting from nucleic acid so identified as being able to complement the *GAI* null mutant a nucleotide sequence encoding the 17 amino acid sequence underlined in Figure 4 or a contiguous 17 amino acid sequence in which at least 10 residues have similarity or identity with the respective amino acid in the corresponding position in the 17 amino acid sequence underlined in Figure 4, more preferably 11, 12, 13, 14, 15, 16 or 17.

The paragraphs beginning at page 34, line 3:

Figure 3: A nucleotide sequence of (SEQ ID NO:1) a *GAI* gene encoding a polypeptide with GAI function.

Figure 4: Primary structure of GAI and gai proteins. The amino acid sequence (SEQ ID NO:2) predicted from the genomic DNA sequence of GAI is shown. The 17 amino acid segment deleted in gai is shown in bold face and double-underlined.

The paragraphs beginning at page 34, line 14:

Figure 6a: Nucleotide sequence of *gai-d1* (SEQ ID NO:3).

Figure 6b: Amino acid sequence of *gai-d1* (SEQ ID NO:4).

Figure 6c: Nucleotide sequence of *gai-d2* (SEQ ID NO:5).

Figure 6d: Amino acid sequence of *gai-d2* (SEQ ID NO:6).

Figure 6e: Nucleotide sequence of *gai-d5* (SEQ ID NO:7).

Figure 6f: Amino acid sequence of *gai-d5* (SEQ ID NO:8).

Figure 6g: Nucleotide sequence of *gai-d7* (SEQ ID NO:9).

Figure 6h: Amino acid sequence of *gai-d7* (SEQ ID NO:10).

The paragraphs beginning at page 37, line 21:

Primer N6 (SEQ ID NO:11): 5'TAG AAG TGG TAG TGG3';

Primer AT1 (SEQ ID NO:12): 5'ACC ATG AGA CCA GCC G3'.

The paragraph beginning at page 38, line 19:

Searches of the DNA and protein sequence databases revealed no domains of obvious functional significance within GAI. *gai* contains a deletion of 51 bp from within the *GAI* ORF. This in-frame deletion results in the absence, in gai, of a 17 amino acid residue segment situated close to the amino terminus of the predicted GAI protein (SEQ ID NO:2) (Figure 4).

The paragraph beginning at page 39, line 5:

A previous publication described the isolation, following γ-irradiation mutagenesis, of *gai* derivative alleles[5]. These alleles, when homozygous, confer a tall phenotype indistinguishable from that conferred by GAI[5]. Sequencing of amplified fragments from several of the derivative alleles (*gai-di*, *gai-d2*, *gai-d5* and *gai-d7*) showed that each contains the 51 bp deletion characteristic of *gai*. Nucleotide and encoded amino acid sequences of these alleles are shown in Figure 6 (SEQ ID NOS:3 to SEQ ID NO:10). They also contain additional mutations that could confer a non-functional gene product (Table 1). The fact that loss of *gai* mutant phenotype is correlated with each of these mutations, together with the reversion data (see above), confirms that *GAI* has been cloned. Furthermore, these results are consistent with predictions that the gai-d alleles would be null alleles[5,6].

IN THE CLAIMS:

49. (Amended) An isolated nucleic acid having a nucleotide sequence coding for a polypeptide of which the amino acid sequence comprises the 17 amino acid sequence

that is underlined in Figure 4 (SEQ ID NO:2) and has at least 90% amino acid sequence identity with the amino acid sequence shown in Figure 4 (SEQ ID NO:2).

50. (Amended) An isolated nucleic acid having a nucleotide sequence coding for a polypeptide of which the amino acid sequence comprises the 17 amino acid sequence that is underlined in Figure 4 (SEQ ID NO:2) and has at least 90% amino acid sequence identity with the amino acid sequence shown in Figure 4 (SEQ ID NO:2), wherein expression of said nucleic acid in a plant results in inhibition of growth of the plant, the inhibition being antagonised by gibberellin (GA).

51. (Amended) An isolated nucleic acid having a nucleotide sequence coding for a polypeptide which comprises the 17 amino acid sequence that is underlined in Figure 4 (SEQ ID NO:2) and which includes an amino acid sequence which has at least 90% identity with the amino acid sequence shown in Figure 4 (SEQ ID NO:2), wherein expression of said nucleic acid complements a *GAI* null mutant phenotype in a plant, such phenotype being resistance to the dwarfing effect of paclobutrazol.

52. (Amended) An isolated nucleic acid that hybridizes [strongly] to the complement of a nucleic acid coding for the amino acid sequence [is] as shown in Figure 4 (SEQ ID NO:2), under the following conditions: hybridization without formamide for 18 hours at 65°C, with washing once with 3 x SSC (1 x SSC is 0.15 M NaCl, 0.015 M sodium citrate), 0.1% SDS for 25 minutes at 65°C, and once with 0.1 x SSC, 0.1% SDS for 25 minutes at 65°C.

53. (Amended) An isolated nucleic acid that hybridizes [strongly] to the complement of a nucleic acid coding for the amino acid sequence shown in Figure 4 (SEQ ID NO:2), under the following conditions: hybridization without formamide for 18 hours at 65°C, with washing once with 3 x SSC (1 x SSC is 0.15 M NaCl, 0.015 M sodium citrate), 0.1% SDS for 25 minutes at 65°C, and once with 0.1 x SSC, 0.1% SDS for 25 minutes at 65°C, wherein expression of said isolated nucleic acid in a plant results in inhibition of growth of the plant, the inhibition being antagonised by gibberellin (GA).

54. (Amended) An isolated nucleic acid that hybridizes [strongly] to the complement of a nucleic acid coding for the amino acid sequence shown in Figure 4 (SEQ

ID NO:2), under the following conditions: hybridization without formamide for 18 hours at 65°C, with washing once with 3 x SSC (1 x SSC is 0.15 M NaCl, 0.015 M sodium citrate), 0.1% SDS for 25 minutes at 65°C, and once with 0.1 x SSC, 0.1% SDS for 25 minutes at 65°C, wherein expression of said isolated nucleic acid complements a *GAI* null mutant phenotype in a plant, such phenotype being resistance to the dwarfing effect of paclobutrazol.

55. (Amended) [An] The isolated nucleic acid according to any one of claims 50, 51, 53 and 54 wherein said plant is *Arabidopsis thaliana*.

56. (Amended) [Nucleic] The nucleic acid according to any one of claims 49 to 54 further comprising a regulatory sequence for expression.

57. (Amended) [Nucleic] The nucleic acid according to claim 56 wherein the regulatory sequence comprises an inducible promoter.

58. (Amended) A nucleic acid vector suitable for transformation of a plant cell and comprising the nucleic acid according to any one of claims 49 to 54.

60. (Amended) [A] The host cell according to claim 59 which is a plant cell.

61. (Amended) [A] The plant cell according to claim 60 having said heterologous nucleic acid within its genome.

62. (Amended) [A] The plant cell according to claim 61 which is comprised in a plant, a plant part or a plant propagule, or extract [or derivative] of a plant.

63. (Amended) A method of producing [a] the cell according to claim 60, the method comprising incorporating said nucleic acid into the cell by means of transformation.

64. (Amended) [A] The method according to claim 63, which comprises recombining the nucleic acid with the cell genome nucleic acid such that it is stably incorporated therein.

65. (Amended) [A] The method according to claim 64 which comprises regenerating a plant from one or more transformed cells.

66. (Amended) [A] The method according to claim 65 comprising sexually or asexually propagating or growing off-spring or a descendant of the plant regenerated from said plant cell.

67. (Amended) A plant comprising [a] the plant cell according to claim 61.

68. (Amended) A method of producing a plant, the method comprising incorporating the nucleic acid according to any one of claims 49 to 54 into a plant cell and regenerating a plant from said plant cell.